PATENT
Docket No. 55943USA1A

SAMPLE PROCESSING APPARATUS, METHODS AND SYSTEMS

Field of the Invention

The present invention relates to sample processing systems and methods. More particularly, the present invention provides apparatus, methods, and systems for processing sample materials.

Background

Many different chemical, biochemical, and other reactions are sensitive to temperature variations. The reactions may be enhanced or inhibited based on the temperatures of the materials involved. Although it may be possible to process samples individually and obtain accurate sample-to-sample results, individual processing can be time-consuming and expensive.

Examples of some thermal processes that may be sensitive to temperature variations include, e.g., the manipulation of nucleic acid samples to assist in the deciphering of the genetic code. *See, e.g.,* T. Maniatis et al. *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory (1982). Nucleic acid manipulation techniques include amplification methods such as polymerase chain reaction (PCR); target polynucleotide amplification methods such as self-sustained sequence replication (3SR) and strand-displacement amplification (SDA); methods based on amplification of a signal attached to the target polynucleotide, such as "branched chain" DNA amplification; methods based on amplification of probe DNA, such as ligase chain reaction (LCR) and QB replicase amplification (QBR); transcription-based methods, such as ligation activated transcription (LAT) and nucleic acid sequence-based amplification (NASBA); and various other amplification methods, such as repair chain reaction (RCR) and cycling probe reaction (CPR). Other examples of nucleic acid manipulation techniques include, e.g., Sanger sequencing, ligand-binding assays, etc.

One approach to reducing the time and cost of thermally processing multiple samples using such techniques is to use a device including multiple chambers in which different portions of one sample or different samples can be processed simultaneously. Although widely accepted standardized systems have been developed using microtiter plates having, e.g., 96, 384 or more wells, to speed the processing of multiple sample, even faster sample processing is still desired.

One disadvantage of such devices is, however, their non-standard format as compare to, e.g., the widely accepted standard microtiter plates. As a result, it may be prohibitive in terms of, e.g., equipment costs, test result acceptance, etc. for a facility to abandon the industry standard processes completely and adopt a new test methodology and new equipment.

Another disadvantage of such an approach is in the limited volume available on such devices, which can make cleanup of reaction products difficult due to the limited storage for cleanup solutions.

Summary of the Invention

The present invention provides apparatus, methods, and systems for processing sample materials that may be presented in a standard microtiter plate. More particularly, the present invention provides a bridge between the standard microtiter plate systems, methods, protocols, etc. with their stationary wells and rotating sample processing devices that allow users to obtain the rapid processing advantages of the newer sample processing devices while retaining the benefits of the standard microtiter plate formats.

For example, the rotating sample processing devices can be used to rapidly and accurately perform required processing of the sample materials by virtue of their rotation. That rotation may be used to expose the processing chambers to energy and/or to assist in transporting the sample material to different areas on the processing devices.

In addition, cleanup of the processed sample materials can be performed off of the sample processing device, thereby mitigating any concerns regarding

available volume of the sample processing device for any cleaning solutions and materials.

A further advantage of the present invention is its amenability to automation to further enhance speed and/or cost of obtaining the desired results.

In one aspect, the present invention provides an apparatus for processing sample materials, the apparatus including a platform having an upper surface and a lower surface; a plurality of stationary fluid chambers opening at the upper surface of the platform; and retention structure occupying a portion of the upper surface of the platform, wherein the retention structure is capable of retaining a rotating multi-chambered processing device proximate the upper surface of the platform.

In another aspect, the present invention provides an apparatus for processing sample materials, the apparatus including a platform having an upper surface and a lower surface; a plurality of stationary fluid chambers opening at the upper surface of the platform; retention structure occupying a portion of the upper surface of the platform; and a processing device located within the retention structure proximate the upper surface of the platform, the processing device including a plurality of process chambers, wherein the processing device is capable of being rotated within the retention structure to move the plurality process chambers.

In another aspect, the present invention provides a method of processing sample material by providing a platform having an upper surface and a lower surface, a plurality of stationary fluid chambers opening at the upper surface of the platform, and retention structure occupying a portion of the upper surface of the platform; providing a processing device in the retention structure proximate the upper surface of the platform, the processing device including a plurality of process chambers; providing sample material in a plurality of the plurality of process chambers on the processing device; delivering energy to the process chambers containing sample material to raise the temperature of the sample materials in the process chambers; and rotating the processing device about an axis of rotation within the retention structure while delivering the energy,

wherein the temperature of the sample materials in the process chambers is controlled as the processing device rotates to process the sample materials.

In another aspect, the present invention provides a method of processing sample material by providing a platform having an upper surface and a lower surface, a plurality of stationary fluid chambers opening at the upper surface of the platform, and retention structure occupying a portion of the upper surface of the platform, wherein the plurality of stationary fluid chambers are arranged in a rectilinear array on the upper surface of the platform; placing a processing device in the retention structure proximate the upper surface of the platform, the processing device including a plurality of process chambers; positioning at least one of the process chambers on the processing device at a transfer site proximate the upper surface of the platform, wherein the location of the transfer site is fixed relative to the stationary fluid chambers; loading sample material in a plurality of the plurality of process chambers on the processing device, wherein the process chambers are loaded while positioned at the transfer site; rotating the processing device about an axis of rotation within the retention structure on a spindle extending through a spindle opening formed through the upper and lower surfaces of the platform; delivering energy to at least some of the plurality of process chambers containing sample material while rotating the processing device to control the temperature of the sample materials in the process chambers, whereby the sample materials are processed; and transferring the sample materials from the process chambers on the processing device to the plurality of stationary fluid chambers on the platform after processing the sample materials; wherein the sample materials in the process chambers are transferred while the process chambers are located at the transfer site.

In another aspect, the present invention provides a system for processing sample material, the system including a workspace including a processing station; at least one platform located within the workspace, each platform having an upper surface and a lower surface, a plurality of stationary fluid chambers opening at the upper surface of the platform, and retention structure occupying a portion of the upper surface of the platform; at least one processing device located within the workspace, each processing device including a plurality of

process chambers, wherein rotation of the processing device within the retention structure on the platform moves the plurality process chambers in a circular pattern; a spindle located at the processing station; and a transfer device operative within the workspace, the transfer device capable of transferring sample material from the processing station to another location within the workspace.

These and other features and advantages of the present invention are described with respect to illustrative embodiments of the invention presented below.

Brief Description of the Drawings

FIGURE 1 is an exploded diagram of one platform and sample processing device according to the present invention.

FIGURE 2 is an assembled view of the platform and sample processing device of Figure 1.

FIGURE 3 is an enlarged cross-sectional view of one fluid chamber on the platform including filter material.

FIGURE 4 is a schematic diagram illustrating the positioning of various features of the apparatus on a rectilinear grid.

FIGURE 5 is a schematic diagram of a system using the platforms and sample processing devices of the present invention.

FIGURE 6 is an exploded diagram of another platform and sample processing device according to the present invention.

FIGURE 7 is an assembled view of the platform and sample processing device of Figure 6.

Detailed Description of Illustrative Embodiments of the Invention

The present invention provides apparatus, methods, and systems for processing sample materials that may be presented in a standard microtiter plate. More particularly, the present invention provides a bridge between the standard microtiter plate systems, methods, protocols, etc. and rotating sample processing devices.

A portion of one illustrative system is depicted in Figures 1 and 2. The depicted portion of the system includes a sample processing device 10 that may preferably be provided in a disc-shaped format such as that depicted. Examples of suitable disc-shaped devices 10 may be found in, for example, U.S. Provisional Patent Application Serial No. 60/214642 filed on June 28, 2000 and titled SAMPLE PROCESSING DEVICES, SYSTEMS AND METHODS (Attorney Docket No. 55266USA99.003) and U.S. Provisional Patent Application Serial No. 60/237,151 filed on even date herewith and titled SAMPLE PROCESSING DEVICES, SYSTEMS AND METHODS (Attorney Docket No. 56047USA29). Among the processing devices described in those references, it may be preferable to use those that include features conducive to automated loading and/or unloading as well as automated processing (e.g., tapered inlet ports, seal systems on output chambers, registration systems, etc.). It should further be noted that the devices described in those references may be manufactured according to the principles described in U.S. Provisional Patent Application Serial No. 60/214508 filed on June 28, 2000 and titled THERMAL PROCESSING DEVICES AND METHODS (Attorney Docket No. 55265USA19.003).

Other processing devices may also be used in connection with the present invention, although they may preferably be modified to incorporate features conducive to automated loading and/or unloading, as well as automated processing. Examples of some potentially useable rotating processing devices include, but are not limited to those described in, e.g., U.S. Patent Nos. 5,160,702 (Kopf-Sill et al.); 5,585,069 (Zanzucchi et al.); 6,030,581 (Virtanen); and ~~6,063589 (Kellog et al.)~~ 6,063,589 (Kellogg et al.); as well as in International Publication No. WO 00/40750 (Orlefors et al.).

A platform 20 is also provided and includes retention structure 22 on its upper surface that is capable of retaining the processing device 10 proximate the upper surface of the platform 20 while the processing device 10 is rotating. The retention structure 22 may preferably be slightly larger than the processing device 10 to allow clearance for the processing device 10 to rotate within the retention structure 22. It may be preferable, but not required, that the retention

structure 22 also be in the same general shape as the thermal processing device 10, e.g., circular for disc-shaped processing device 10.

It may be preferred that the retention structure 22 be provided in the form of a cavity as depicted in Figures 1 and 2. On one alternative, the retention structure on a platform 20 may be provided in the form of, e.g., a series of raised posts or protrusions that cooperate to retain the processing device 10 within a desired area on the upper surface of the platform 20.

In one variation, the retention structure may allow for placement and removal of a processing device 10, such as the retention structure 22 illustrated in Figures 1 and 2. As a result, the platform 20 may be used with multiple processing devices 10 that may be located in and removed from the retention structure as needed. In another alternative, such retention structure may allow the user to select a particular processing device 10 for use with the platform 20.

In another variation, the retention structure may be used to retain a captive processing device 10 within a specified area on the upper surface of the platform 20. As used in connection with the present invention, a "captive" processing device means that the processing device cannot be top-loaded into the retention structure without removing a portion of the platform 20 or somehow distorting the shape of the processing device 10. A captive processing device would be retained within the retention structure even if the platform 20 were oriented such that the upper surface faced the ground.

The depicted platform 20 also includes optional sample fluid chambers 24 that may be used as a staging area for sample materials to be introduced onto the processing device 10. The fluid chambers 24 may also contain one or more reagents that may be used on the processing device 10. The fluid chambers 24 may preferably be arranged in a rectilinear array that is similar in form to arrays of wells found on a standard microtiter plate having, e.g., 96, 384, or more wells.

The platform 20 also includes fluid chambers 26 to be used to receive processed sample material removed from the processing device 10. The fluid chambers 26 may include filter material 27 within the chamber 26 (see Figure 3). The fluid chambers 26 may also include a drain port 28 opening at the lower surface of the platform 20 such that sample material introduced into the chamber

26 may pass through the fluid chamber 26. If filter material 27 is present within the chamber 26, then the sample material is filtered during its passage through the chamber 26.

The fluid chambers 26 on the platform 20 may preferably be arranged in a rectilinear array that is similar in form to arrays of wells found on standard microtiter plates. Further, the fluid chambers 26 are also preferably spaced at intervals compatible with a standard microtiter plate such that wells on a standard microtiter plate located beneath the platform 20 would be aligned with any drain ports of the output wells 26. As a result, processed sample materials removed from the device 10 and transferred to the fluid chambers 26 could be passed through the drain ports of the fluid chambers 26 and into the wells on a standard microtiter plate for additional processing using conventional equipment and procedures.

Also depicted in Figures 1 and 2 is a support carriage 40 including alignment structure 42 for receiving the platform 20. The support carriage 40 may preferably include an opening 44 to allow for passage of processed sample materials from the fluid chambers 26 to a standard microtiter plate located beneath the support carriage 40. The alignment structure 42 may include sloped surfaces as depicted to assist in guiding the platform 20 into position on the support carriage 40.

A spindle 30 is also depicted in Figures 1 and 2 that can be used to rotate the processing device 10 to facilitate processing of the sample materials located thereon. The spindle 30 preferably extends upward through the support carriage 40 and through a spindle opening 23 in the retention structure 22 of the platform 20 (when the plate 20 is located on the carriage 40).

A chuck 32 adapted to mate with the processing device 10 is preferably provided on the end of the spindle 30. The chuck 32 preferably includes a support plate 34 adapted to support the device 10 and at least one, preferably multiple, locking arms 36 in the form of levers that swing outward to retain the device 10 on the chuck 32 as the spindle 30 rotates. The arms 36 may preferably be weighted (or otherwise constructed) such that when the spindle 30 is not

rotating, the arms 36 are retracted to allow for placement and removal of the device 10 without hindrance from the arms 36.

In the use of the combination of platform 20 and processing device 10, it may be preferred to position a processing chamber on the processing device 10 at a transfer site proximate the upper surface of the platform 20. A "transfer site" as used herein, is a location at a fixed position relative to the stationary fluid chambers 26. It may be preferred that the stationary fluid chambers 26 and the transfer site 25 be positioned according to a common reference system, e.g., on a rectilinear grid, according to polar coordinates, etc. It may further be preferred that all of the sample fluid chambers 24, stationary fluid chambers 26, transfer site 25 and the location at which loading chambers 16 are positioned for loading be defined by a common reference system.

Referring to Figure 4, one example of a suitable reference system is depicted in which the stationary fluid chambers 26 are located at intersection points on a rectilinear grid, while the transfer site 25 is located at another of the intersection points on the grid. Because the processing device 10 rotates within the retention structure on the platform, different process chambers 12 on the processing device 10 can be indexed into position at the transfer site 25. It may also be preferred that any sample fluid chambers 24, as well as loading chambers 16 on the processing device 10 be positioned at locations defined by a rectilinear array.

Positioning of the processing device 10 to accomplish, e.g., providing the processing chambers 12 on the processing device 10 at the transfer site 25 may be accomplished by any suitable technique. A variety of registration systems and methods are discussed in, e.g., U.S. Provisional Patent Application Serial No. 60/214,642 filed on June 28, 2000 and titled SAMPLE PROCESSING DEVICES, SYSTEMS AND METHODS (Attorney Docket No. 55266USA99.003).

One example of a registration system including complementary structures is depicted in Figures 1 and 2, where one or more of the arms 36 may cooperate with a keyed slot 14 on the device 10 for registering the rotational position of the processing device 10 on the spindle 30 and, therefore, within the retention

structure 22 on the platform 20. Such structure can be used to fix the rotational position of the processing device 10 on the spindle 30, provided for accurate indexing of the processing device 10 to put the various features on the processing device 10 in the desired positions.

The apparatus depicted in Figures 1 and 2 may preferably be used in connection with a variety of transfer devices available from a variety of manufacturers including, but not limited to: Beckman Coulter, Inc. (Fullerton, California), Packard Instrument Company (Meriden, Connecticut), Tomtec (Hamden, Connecticut), MWG-Biotech Inc. (High Point, North Carolina), and Qiagen (Valencia, California). Such automated transfer devices typically include pick-and place robotic technology and can be outfitted with a processing station including the support carriage 40 and spindle 30 adapted to receive a platform 20 and associated thermal processing device 10.

One such system is depicted in Figure 5 and includes a controller 100, transfer device 102, supplies 104 (which may include, e.g., platforms, thermal processing devices, pipette tips, cleanup materials, sample materials, etc.), a processing station 106 (including, e.g., a support carriage 106a, spindle 106b, and source of electromagnetic radiation 106c) and an unloading station 108. All of these components may preferably be located within a workspace 101.

In use, the processing station 106 can be loaded with the necessary materials from supplies 104 (e.g., a platform, sample materials, processing device, etc.) using the transfer device 102. Sample materials can then be processed at the processing station 106, with the transfer device 102 being used to transfer sample materials to the desired locations (e.g., from sample fluid chambers on the platform to loading chambers on a processing device and/or from process chambers on the processing device to stationary fluid chambers on the platform, etc.).

After processing at the processing station 106, the platform (with processed sample material) may be moved to, e.g., the unloading station 108 using the transfer device 102, where the processed sample materials may cleaned up using supplies 104 (delivered by the transfer device 102). The sample

materials may then be transferred to a standard microtiter plate at the unloading station 108 for further processing of the sample materials.

In some embodiments, it may be preferred to provide the processing station 106 in the form of one of the systems described in, e.g., U.S. Provisional Patent Application Serial No. 60/214,642 filed on June 28, 2000 and titled SAMPLE PROCESSING DEVICES, SYSTEMS AND METHODS (Attorney Docket No. 55266USA99.003) (see, e.g., Figure 9 and the corresponding description in that application) or U.S. Provisional Patent Application Serial No. 60/237,151 filed on even date herewith and titled SAMPLE PROCESSING DEVICES, SYSTEMS AND METHODS (Attorney Docket No. 56047USA29).

Furthermore, in another variation the platforms of the present invention may be provided with only a retention structure adapted to receive a rotating processing device, i.e., in the absence of any fluid chambers for staging sample materials or receiving processed sample materials from the processing devices. The rectilinear shape of the preferred platforms allows the rotating processing devices to be used in largely conventional robotic transfer devices. In such a system, it may be desirable, e.g., to provide pipettes or other fluid transfer apparatus that include some filtering structure within them to filter the processed sample materials as they are drawn from the processing devices. The filtered sample materials can then be deposited in the wells of, e.g., standard microtiter plates for conventional processing. Examples of some fluid transfer apparatus that may include materials to clean up samples are described in, e.g., U.S. Patent No. 6,048,457 (Kopaciewicz et al.).

Turning now to Figures 6 and 7, where an alternative apparatus according to the present invention is depicted. The depicted apparatus is useful in those systems and methods in which vacuum is used to remove the processed sample materials from the platform 120. The apparatus includes a platform 120, a vacuum manifold collar 150, and a manifold base 170 in between which a standard microtiter plate 160 is located when the collar 150 and base 170 are assembled. Together, the vacuum manifold collar 150 and manifold base 170 provide a vacuum manifold useful in extracting sample material from the

platform 120 and transferring it to the microtiter plate 160 for processing using conventional processes and equipment.

The platform 120 includes retention structure 122 similar to that described with respect to platform 20 above. A spindle opening 123 is included within the retention structure 122 to receive a spindle adapted to rotate a processing device located therein (not shown).

The platform 120 also includes optional sample fluid chambers 124 that may be used as a staging area for samples to be introduced onto a processing device. The fluid chambers 124 may also contain one or more reagents. The fluid chambers 124 may preferably be arranged in a rectilinear array that is similar in form to arrays of wells on a standard microtiter plate.

The platform 120 also includes stationary fluid chambers 126 to be used to receive processed sample material removed from a processing device. The fluid chambers 126 may include filter material. The fluid chambers 126 on the platform 120 may preferably be arranged in a rectilinear array that is similar in form to arrays of wells found on standard microtiter plates.

Further, the fluid chambers 126 are also preferably spaced at intervals compatible with the spacing of the wells 162 on the microtiter plate 160 such that each of the fluid chambers 126 is located above one of the wells 162 in the microtiter plate 160. It may be preferred that the fluid chambers 126 include extended drain ports 128 adapted to extend at least partially into the microtiter plate wells 162. The extended drain ports 128 may assist in preventing cross-contamination during the transfer of materials from the fluid chambers 126 on the platform 120 to the microtiter plate wells 162.

The vacuum manifold collar 150 preferably includes a seat 152 adapted to receive the lower surface of platform 120. A gasket 156 may preferably be located within the seat 152 to assist in sealing around the lower surface of platform 120 when a vacuum is supplied to the manifold. The collar 150 also includes an opening 154 through which the extended drain ports 128 on the fluid chambers 126 extend when the apparatus is assembled. The manifold base 170 may also preferably include a gasket 172 to assist in sealing the manifold collar 150 to the manifold base 170.

During use, a vacuum source may be connected to the assembled manifold base 170 and collar 150 to provide a negative pressure that draws processed sample material in the fluid chambers 126 into the microtiter plate wells 162. If the fluid chambers 126 contain filter material, then the processed sample materials in the fluid chambers 126 may be filtered during transfer to the microtiter plate 160. After the transfer is completed, the microtiter plate 160 can be removed and processed using conventional methods and techniques.

One alternative to the use of vacuum in connection with the apparatus depicted in Figures 6 and 7 is the use of positive pressure from above the fluid chambers 126 to force the sample materials in the fluid chambers down through the drain ports 128 and into the microtiter plat 160. In such an apparatus, it may be necessary to provide a pressure manifold that seals about the top surface of the platform 120 around the openings of the fluid chambers 126.

Patents, patent applications, and publications disclosed herein are hereby incorporated by reference as if individually incorporated. It is to be understood that the above description is intended to be illustrative, and not restrictive. Various modifications and alterations of this invention will become apparent to those skilled in the art from the foregoing description without departing from the scope of this invention, and it should be understood that this invention is not to be unduly limited to the illustrative embodiments set forth herein.